PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RJS/B45323	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11810	International filing date *(day/month/year)* 21.10.2003	Priority date *(day/month/year)* 23.10.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/569		
Applicant GLAXOSMITHKLINE BIOLOGICALS SA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.04.2004	20.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Diez Schlereth, D Telephone No. +49 89 2399-7488

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11810

I. **Basis of the report**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-9 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5,7-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5,7-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5,7-8
	No:	Claims	

2. Citations and explanations

   see separate sheet

item III

No meaningful International Preliminary Examination Report can be established for the subject-matter of claim 6 (Art. 34 (4) (a) (ii) and (b) PCT), for the following reasons: this claim does not meet the requirements of Art. 6 PCT insofar that the kit does not comprise all components (technical features), which are necessary to carry out the method of claim 1 (PCT Guidelines III-4.3(ii)). It is further noted that this requirement has to be fulfilled for complying also with the requirements of Rules 13.1 and 13.2 PCT regarding unity of invention.

item V

1.) Reference is made to the following documents:

D1: H. Yamamoto et al (1997) Biologicals 25, 373-380
D2: EP-A-0 339 667
D3: J. B. Katz et al (1989) J. Virol. Meth. 25, 101-108

2.) The subject-matter of claims 1-5 (complete) and 7-8 (partially, see item III above) is considered to be novel and inventive within the sense of Art. 33 (2) and (3) PCT, for the following reasons:

D1 (closest state of the art, see p. 373-375) discloses a method for quantifying the amount of antigen in Hepatitis B vaccines prepared by adsorbing hepatitis B surface antigen (HBsAg) on $Al(OH)_3$. The method comprises (i) contacting the vaccine sample with a phosphate-citrate basic buffer (pH = 8.5) for desorbing the antigen, (ii) diluting the sample in a PBS buffer containing 0.5% casein as blocking agent, (iii) contacting the diluted sample with a microtiter plate coated with anti-HB pAb, and detecting binding with mAb/HRP-conjugated immunoglobulin (p. 375).

D2 discloses a method for determining the amount of antigen in Hepatitis A vaccines prepared by adsorbing HA antigen on $Al(OH)_3$. The method comprises (i) contacting the vaccine sample with a phosphate-citrate buffer (same buffer as in D1) for desorbing the antigen and determining the desorbed antigens by an ELISA using plates coated with anti-HAV serum and BSA as blocking agent (p. 5, l. 40-45 and p. 9, l. 30-35).

D3 discloses an antigen capture ELISA for determining the antigeninc content of $Al(OH)_3$-adjuvated vaccines which circumvents the interferences produced by the aluminium salt.

The method comprises (i) coating a microtiter plate with antibodies using a coating buffer with pH 9.6 (ii) washing the plates and blocking them using dry milk as blocking agent, (iii) contacting them with a vaccine sample diluted with a PBS buffer pH 7.2, and (iv) detecting binding with an alkaline phosphatase conjugate (see abstract and p. 102-103).

The method of claim 1 differs from that of D1 in that the antigen is contacted with the immunoglobulin in the presence of a basic buffer **before** carrying out the steps of adding the blocking agent, and detecting the binding of antibody to the antigen.

By contrast with other methods known from the prior art, the method of claim 1 allows to determine accurately the amount of HBsAg present in a vaccine sample containing $Al(OH)_3$.

D1-D3 disclose methods in which the immunoglobulin is brought into contact with the antigen after having added the blocking agent (in the detection step). Thus, the skilled person, equipped with the teaching of D1-D3 would not be motivated to modify the method of D1 and arrive at a method as claimed in claims 1 (and 2-5, 8 as dependent thereon) with the purpose to improve the performance of the method in samples containing $Al(OH)_3$.

Analogous arguments apply for the subject-matter of claims 7-8, which relates to kits that are specially adapted to carry out the method of claim 1.